available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Attentional control during the transient updating of cue information

Luiz Pessoa[a,*], *Andrew Rossi*[b], *Shruti Japee*[c], *Robert Desimone*[d], *Leslie G. Ungerleider*[c]

[a]*Department of Psychological and Brain Sciences, Indiana University, 1101 East Tenth Street Bloomington, IN 47405, USA*
[b]*Division of Neuroscience and Basic Behavioral Science, NIMH, Bethesda MD, USA*
[c]*Laboratory of Brain and Cognition, NIMH, Bethesda, MD, USA*
[d]*McGovern Institute, Massachusetts Institute of Technology, Cambridge, MA, USA*

ARTICLE INFO

Article history:
Accepted 5 October 2008
Available online 22 October 2008

Keywords:
Attention
Vision
fMRI

ABSTRACT

The goal of the present study was to investigate the neural correlates of top-down control of switching behavior in humans and to contrast them to those observed during switching behavior guided by bottom-up mechanisms. In the main experimental condition (*color-cue*), which was guided by top-down control, a central cue indicated the color of a peripheral grating on which the subject performed an orientation judgment. For *switch trials*, the color of the cue on the current trial was different from the color on the previous trial. For *non-switch trials*, the color of the cue on the current trial was the same as the color in the preceding trial. During a control condition (*pop-out*), which was guided by bottom-up saliency, the target grating was defined by color contrast; again both switch and non-switch trials occurred. We observed stronger evoked responses during the color-cue task relative to the pop-out task in the inferior parietal lobule (IPL), frontal eye field (FEF), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG). The contrast of switch vs. non-switch trials revealed activations in regions that were engaged when there was a *change* in the identity of the target. Collectively, switch trials evoked stronger responses relative to non-switch trials in fronto-parietal regions that appeared to be left lateralized, including left intraparietal sulcus (IPS) and left MFG/IFG. Task by trial type interactions (switch>non-switch during color-cue relative to pop-out) were observed in several fronto-parietal regions, including IPS, FEF, MFG and IFG, in addition to regions in visual cortex. Our findings suggest that, within the fronto-parietal attentional network, the IPS and MFG/IFG appear to be most heavily involved in attentive cue updating. Furthermore, several visual regions engaged by oriented gratings were strongly affected by cue updating, raising the possibility that they were the recipient of top-down signals that were generated when cue information was updated.

1. Introduction

The prefrontal cortex (PFC) has been hypothesized to be at the highest level of a cortical hierarchy dedicated to the representation and execution of actions (Fuster, 1997; Miller, 2000). Consistent with this view, the PFC is known to be involved in a host of "control functions", including working memory, task switching, and error monitoring (Stuss and Knight, 2002b). In

* *Corresponding author.*
E-mail address: lpessoa@indiana.edu (L. Pessoa).

0006-8993/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2008.10.010

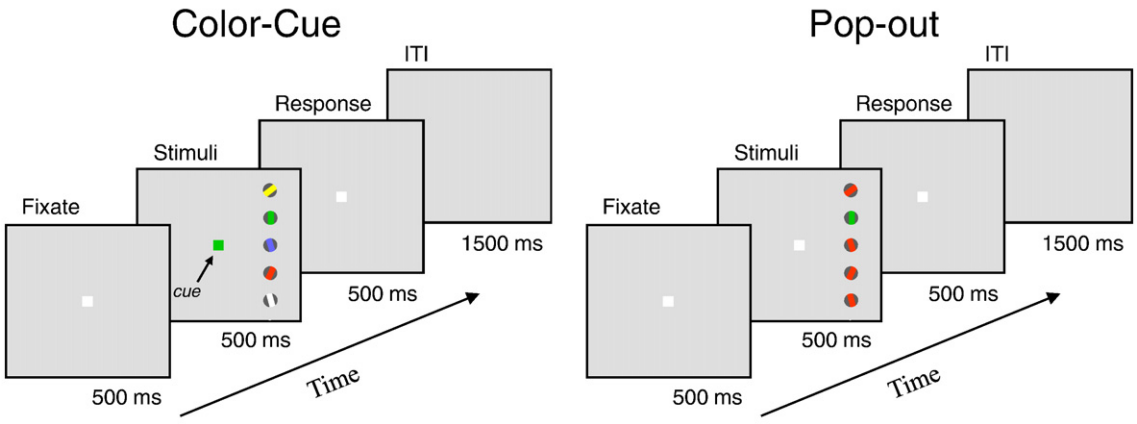

Fig. 1 – Experimental paradigm. During both the color-cue (left) and the pop-out (right) conditions, switch trials occurred at random during the block. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

addition, the PFC is believed to be part of a distributed network that controls attention and is important, in particular, in the goal-directed ("top-down") selection of stimuli and responses (Desimone and Duncan, 1995; Corbetta et al., 2000; Kastner and Ungerleider, 2000; Everling et al., 2002; Pessoa et al., 2003).

Recent progress in the understanding of attentional top-down control comes from neuroimaging studies in humans that have investigated the control of attention to spatial locations and the control of attention to objects (Yantis and Serences, 2003; Serences and Yantis, 2006). Relatively less is known, however, about the control of attention involved in *updating* cue-related information. In a recent study, Rossi et al. (2007) investigated the role of the PFC in top-down updating by investigating the impact of PFC lesions on such functions in macaque monkeys. In one experiment, they investigated the effect of PFC lesions on the monkeys' ability to utilize cue information as a function of the frequency with which the cue was updated. A central cue was used to indicate the color of a peripheral target grating on which the monkey was to perform an orientation judgment. Their findings revealed that the monkeys' impairment in performing the orientation judgment was smallest when the central cue changed infrequently and increased with more frequent changes (i.e., when the top-down load was the greatest). At the same time, the PFC did not appear to be involved in stimulus selection when a target stimulus was defined by "bottom-up" salience. Specifically, when the target was defined as the "odd-man out" (e.g., a green grating among red gratings), impairments in performance did not vary as a function of the frequency with which the target changed.

In their study, Rossi et al. removed extensive portions of the PFC, including dorsolaterally Brodmann areas 9 and 46, ventrolaterally Brodmann areas 12 and 45, and posteriorly the frontal eye field (FEF, Brodmann area 8a); the medial PFC and orbital PFC were spared. Thus, while the study of Rossi et al. revealed that some part of lateral PFC is important for top-down control, it was not possible to more precisely localize the region(s) responsible for the deficit. In addition, because the lesions were confined to the PFC, it was unclear whether other brain regions, such as parietal cortex, were involved in top-down updating in their task.

The goal of the present study was to investigate the neural correlates of top-down attentional updating in humans by employing the same paradigm employed by Rossi et al. (2007). Subjects performed the task during functional magnetic resonance imaging (fMRI). In the main experimental condition, which we called *color-cue*, a central cue indicated the color of a peripheral grating on which the subject performed an orientation judgment (Fig. 1, left). The central cue was a red, green, or blue square. For *switch trials*, the color of the cue on the current trial was different from the color on the previous one. For *non-switch trials*, the color of the cue on the current trial was the same as the color in the preceding trial. Switch and non-switch trials occurred in random order. Because the cue was present in every trial, the contrast of switch and non-switch trials was expected to reveal brain regions involved in the updating of cue-related information. In addition, based on the results by Rossi et al. with monkeys, we expected such *endogenous* cue updating to engage different regions relative to those that would be observed when targets were determined in a bottom-up fashion. To test this prediction, like in the experiment by Rossi et al., we included a *pop-out* condition in which the target grating was defined by color contrast. Specifically, the target grating was the color singleton appearing within an array of gratings with the same color but different from the target (Fig. 1, right). For the pop-out condition, the central cue was thus uninformative.

2. Results

2.1. *Behavioral results*

Due to a technical problem, reaction times (RTs) were not recorded during fMRI scanning. We thus tested 10 subjects in an additional experiment outside the scanner and submitted the results to a repeated-measures analysis of variance (ANOVA). Such analysis revealed significant main effects of task ($p<0.01$) and trial type ($p<0.005$), but no significant inter-

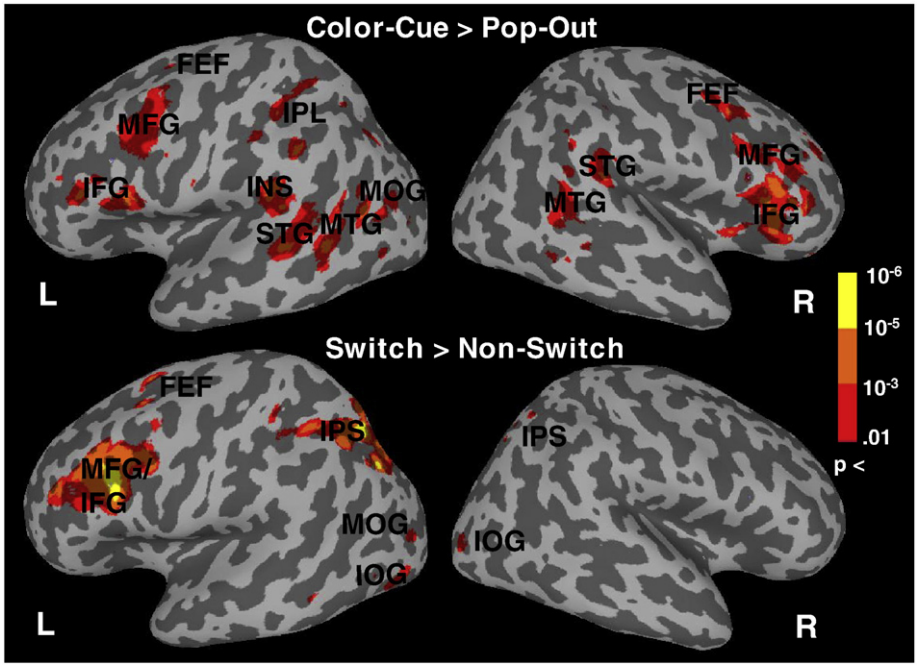

Fig. 2 – Group maps displaying color-cue > pop-out (top) and switch > non-switch (bottom). Data are illustrated on inflated brains. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

action ($p = 0.8$): Mean RTs during color-cue trials (715 ms) were significantly faster than RTs during pop-out trials (731 ms); mean RTs during non-switch trials (718 ms) were significantly faster than RTs during switch trials (731 ms).

2.2. *Color-cue vs. pop-out task*

First, we investigated the main effect of task on brain activation by contrasting color-cue vs. pop-out conditions (Fig. 2). Responses evoked during color-cue trials were stronger than during pop-out trials in several fronto-parietal regions. These regions included, bilaterally, the inferior parietal lobule (IPL), frontal eye field (FEF), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG). In addition, visual regions in the left middle occipital gyrus (MOG) and, bilaterally, middle temporal gyrus (MTG) and superior temporal gyrus (STG) were more strongly activated during the color-cue vs. pop-out task. We did not observe any regions in which responses evoked during pop-out trials were stronger than during color-cue trials. For a complete list of activations and their coordinates, see Table 1.

2.3. *Switch trials vs. non-switch trials*

Next, we compared switch to non-switch trials (pooled across tasks); see Fig. 2 and Table 1. Stronger responses evoked during switch trials were observed in the left intraparietal sulcus (IPS) and left MFG/IFG. These activations were quite extensive; the IPS activation followed the sulcus from $y = -76$ to $y = -48$ and the MFG/IFG activation extended from $y = -5$ to $y = 36$. Smaller foci of activation included the right IPS and left FEF. In addition, visual regions in the MOG and IOG (both bilaterally) and in the left fusiform gyrus (FG) were more strongly activated during switch vs. non-switch trials. Finally, stronger responses for non-switch trials relative to switch trials were observed in the right insula.

2.4. *Task by trial type interaction*

We also probed the contrast of switch vs. non-switch trials during the color-cue task and, separately, during the pop-out task. As shown in Fig. 3 and Table 1, a similar set of fronto-parietal regions were more vigorously recruited during switch vs. non-switch trials during both types of task. Visual inspection suggested that some regions, such as the IPS and MFG/IFG, exhibited stronger switch-related differential activation during the color-cue task relative to the pop-out task. To formally assess such differences, we probed for task by trial type interactions (Fig. 3, Table 2). Regions for which the difference (switch vs. non-switch) was greater during color-cue trials relative to pop-out trials included the following fronto-parietal sites: left IPS, left FEF, left MFG/IFG, and right IFG. Interestingly, several sites in visual cortex were also observed, including left MOG, left IOG and inferior temporal gyrus (ITG), right FG, and MTG. Fig. 4 shows average evoked responses for switch and non-switch trials during both color-cue and pop-out tasks for some of the regions listed above for which there were significant interaction effects. No other significant interactions were observed (e.g., those involving non-switch > switch).

3. Discussion

3.1. *Task-related activations: color-cue vs. pop-out*

The color-cue and pop-out tasks were designed to engage goal directed, top-down processes on the one hand, and reactive, bottom-up processes on the other. Accordingly, we anticipated

Table 1 – Talairach coordinates of local maxima of areas differentially active for various task conditions

Region		Side	Coordinates			T-statistic
			X	Y	Z	
Color-cue > pop-out						
Occipital						
	Posterior MOG	L	−21	−94	−2	3.59
	MOG	L	−41	−72	−2	3.46*
Temporal						
	MTG	L	−47	−59	10	4.0[C]
	MTG	R	47	−40	10	3.49[C]
	STG	L	−51	−41	13	3.78*[C]
	STG	R	51	−37	15	3.61[C]
	Insula	L	−50	−34	24	4.17
Parietal						
	IPL	L	−47	−32	26	4.16*
	IPL	R	43	−39	30	3.30*
Frontal						
	MFG	L	−37	−3	43	3.48*,[C]
	MFG	R	35	2	35	3.75*,[C]
	FEF	L	−36	−4	41	3.3*,[C]
	FEF	R	40	−4	45	3.1*,[C]
	IFG	L	−50	8	19	3.85*,[C]
	IFG	R	46	27	11	4.34[C]
Other						
	Caudate	L	−18	8	21	3.7*,[C]
	Caudate	R	15	8	19	3.2[C]
	Thalamus (pulvinar)	L	−17	−24	16	3.0*,[C]
Switch > non-switch						
Occipital						
	MOG/IOG	L	−36	−77	−9	3.58*,[C]
	MOG/IOG	R	32	−79	−3	3.39*
	FG	L	−29	−56	−10	3.64*,[C]
Temporal						
	ITG	L	−58	−44	−7	3.18
Parietal						
	IPS/precuneus	L	−26	−67	33	6.93*,[C]
	IPS/precuneus	R	30	−59	39	3.25*
Frontal						
	MFG/IFG	L	−35	10	31	6.37*,[C]
	FEF	L	−21	0	57	4.0*,[C]
Non-switch > switch						
Temporal						
	Insula	R	48	−6	−2	3.28
Color-cue (switch > non-switch)						
Occipital						
	MOG/IOG	L	−35	−72	18	4.04*,[C]
	MOG/IOG	R	33	−84	−5	3.58*
	FG	L	−37	−79	−13	5.57*,[C]
	FG	R	35	−54	−20	3.37*
Parietal						
	IPS/precuneus	L	−25	−67	35	6.94*,[C]
	IPS/precuneus	R	29	−67	31	3.29*
Frontal						
	MFG/IFG	L	−36	11	31	6.75*,[C]
	MFG	R	34	−9	42	3.30*
	FEF	L	−23	3	52	4.52*,[C]
	FEF	R	22	5	42	3.29*
Pop-out (switch > non-switch)						
Parietal						
	IPS/precuneus	L	−28	−67	32	5.73*,[C]
Pop-out (switch > non-switch)						
Frontal						
	MFG/IFG	L	−42	0	35	6.07*,[C]
Pop-out (non-switch > switch)						
Frontal						
	Medial FG	L	−5	51	17	3.07
	Medial FG	R	11	60	12	3.68
	Insula	R	45	−3	−10	3.67

Abbreviations: FG: fusiform gyrus; IFG: inferior frontal gyrus; IOG: inferior occipital gyrus; IPL: inferior parietal lobule; IPS: intraparietal gyrus; FEF: frontal eye field; MFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; STG: superior temporal gyrus. *: active at $p<0.001$ (uncorrected) in all-task vs. baseline map; [C]: survives cluster-based thresholding at $p<0.01$, corrected (cluster radius = 5 mm).

that fronto-parietal regions important for the general control of attention would be more strongly recruited during the color-cue condition relative to the pop-out condition. This was indeed the case. We observed stronger evoked responses during the color-cue task relative to the pop-out task in the IPL, FEF, MFG, and IFG. Such activations show a considerable degree of overlap with the attentional network involved in voluntary (endogenous) orienting of attention (Corbetta et al., 2000; Hopfinger et al., 2000b,a; Kastner and Ungerleider, 2000; Marois et al., 2000; Giesbrecht et al., 2003; Marois et al., 2004; Peers et al., 2005). The FEF, in particular, is consistently observed in brain imaging studies during endogenous attention conditions (Rosen et al., 1999; Mayer et al., 2004; Kincade et al., 2005). Note that such activations could not be due to RT effects because responses during the color-cue condition were faster than during the pop-out condition. Instead, such differential activations reflected differences between top-down and bottom-up processes.

An unexpected finding of the present study was the observation of stronger evoked responses in the right MTG and STG during the color-cue relative to the pop-out task. This result was at first surprising because these regions of the temporo-parietal junction (TPJ) have been reported to be more strongly involved in stimulus-driven attentional control of the kind that may have been engaged during the pop-out task (Corbetta and Shulman, 2002). However, the TPJ appears to be more robustly driven by reorienting mechanisms, such as during the processing of an invalidly cued central (endogenous) cue (Kincade et al., 2005), which may explain why we did not observe strong TPJ responses during the pop-out task. In addition, our results suggest that some TPJ sites may be engaged during the top-down control of attention, too, as during the target selection of the color grating signaled by the central cue stimulus.

3.2. *Brain regions triggered by switch trials*

The contrast of switch vs. non-switch trials revealed activations in regions that were engaged when there was a *change* in

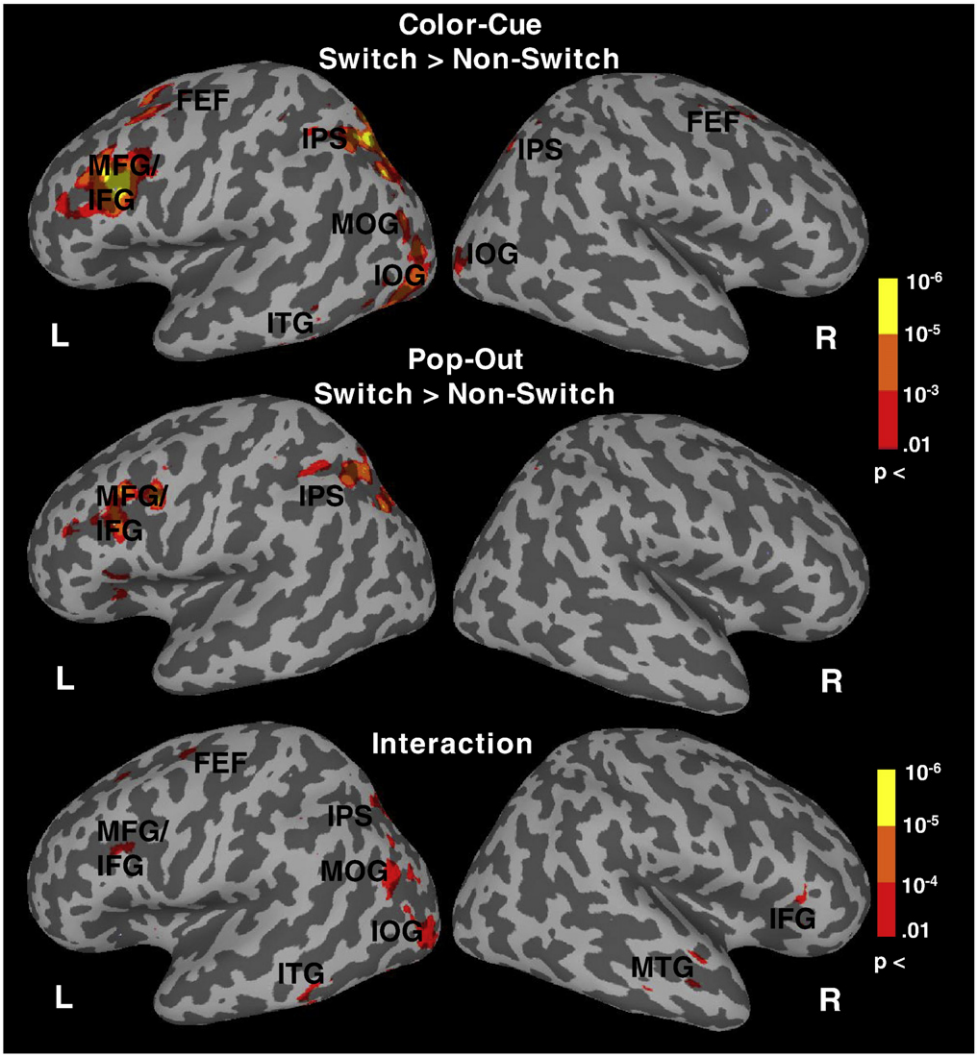

Fig. 3 – Group maps displaying switch > non-switch during the color-cue task (top), switch > non-switch during the pop-out task, and the task by trial type interaction (bottom). Data are illustrated on inflated brains. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the identity of the target. Such change could be signaled either by a change in the color of the cue (color-cue condition) or by a change of the target color as defined by the color singleton (pop-out condition). Collectively, switch trials evoked stronger responses relative to non-switch trials in fronto-parietal regions that appeared to be left lateralized. In particular, extensive activations were observed in the left IPS and left MFG/IFG.

In a series of studies, Yantis et al. investigated the neural correlates of switching the spatial focus of attention and of switching object-based attention (Serences and Yantis, 2006). Switches of spatial attention engaged the right superior parietal lobule (SPL), while object-related switches engaged more medial aspects of the SPL. In our own study, switch trials involved updating information of the color of the target grating. During both color-cue and pop-out switches, target updating engaged extended regions in the left parietal lobe and left MFG/IFG. While these activations were near the sites reported by Yantis et al., they appeared to involve different cortical territories; see also Shomstein and Behrmann (2006).

An extensive literature investigating executive control suggests that dorsolateral PFC (DLPFC) is more strongly recruited during conditions requiring greater control (Cohen et al., 2000; MacDonald et al., 2000; Miller and Cohen, 2001; Casey et al., 2002; Durston et al., 2003). In addition, fMRI studies in humans often show activation of prefrontal regions in tasks in which subjects must switch between responses, switch between tasks, or switch their attention between different stimuli (Dreher and Berman, 2002; Braver et al., 2003; Dreher and Grafman, 2003; Hampshire and Owen, 2006; Slagter et al., 2006). In monkeys, PFC cells appear to switch their response properties between different tasks, and even between different phases of the same task (White and Wise, 1999; Asaad et al., 2000; Buschman and Miller, 2007). Our finding of greater MFG/IFG recruitment during switch vs. non-switch trials is consistent with the role of the DLPFC in behavioral regulation during a switch trial. Interestingly, in the current study, we did not observe differential activation in the anterior cingulate cortex (ACC), possibly because our task did not involve conflict (MacDonald et al., 2000).

Table 2 – Talairach coordinates of local maxima of areas showing interaction between switch and non-switch and color-cue and pop-out

Region	Side	Coordinates			F-statistic
		X	Y	Z	
Interaction: [color-cue (switch > non-switch)] > [pop-out (switch > non-switch)]					
Occipital					
IOG	L	−35	−83	−11	19.84*,C
MOG	L	−44	−67	18	18.34C
FG	R	35	−51	−18	13.45*
Temporal					
MTG	R	54	−10	−13	13.03
ITG	L	−60	−40	−16	11.87
Parahippocampal G	R	36	−19	−23	25.09
Parietal					
IPS/precuneus	L	−28	−72	33	17.09*
Frontal					
MFG/IFG	L	−34	10	27	13.16*
IFG	R	51	22	5	12.77*
SFG	L	−18	10	39	10.19
FEF	L	−21	−15	44	15.29*

Abbreviations: SFG: superior frontal gyrus (other abbreviations as in Table 1). *: active at $p<0.001$ (uncorrected) in all-task vs. baseline map; C: survives cluster-based thresholding at $p<0.01$, corrected (cluster radius = 5 mm).

3.3. *Task by trial type interaction*

A central goal in the present study was to determine brain regions engaged during the updating of an *endogenous* cue (i.e., during the color-cue task). To probe this question, we determined brain activations associated with the interaction of task and trial type. Specifically, we determined regions in which the difference between switch and non-switch trials was greater during the color-cue task relative to the pop-out task. Because both types of trials involved a change in the target grating, such a contrast isolated regions that are important for endogenous updating. Note that no significant task by trial type interaction effect was observed behaviorally; thus RT differences did not drive the observed activations.

Task by trial type interactions were observed in several fronto-parietal regions, including the IPS, FEF, MFG and IFG. As stated before, these regions are thought to be important sites involved in the control of attention. Our findings reveal, furthermore, that these regions are also important for the updating of endogenous cue information. Interestingly, evidence from a recent monkey neurophysiological study comparing the role of PFC and parietal cortex in visual search (a top-down attention task) versus a pop-out task, suggested different roles for these regions during attentional control (Buschman and Miller, 2007). PFC cells showed earlier attentional effects in the visual search task whereas posterior parietal cells showed earlier attentional effects during the pop-out task.

Task by trial interactions were observed not only in fronto-parietal "control" areas, but also in several visual regions, namely, the left MOG, left IOG, and right FG. Therefore, such visual activations were not simply due to the task performed or trial type, but depended instead on the combination of the color-cue task and switch trials. We suggest that such activations may reflect top-down signals from control regions upon the updating of the cue information. For anterior visual areas with bilateral visual inputs, these top-down signals may go to visual areas in either or both hemispheres.

Single-cell recording studies have shown that spontaneous (baseline) firing rates are 30–40% higher for neurons in areas V2 and V4 when a monkey is cued to attend covertly to a location within the neuron's receptive field (RF) in expectation of a stimulus but before it is presented there; that is, in the absence of visual stimulation (Luck et al., 1997). This increased baseline activity, termed the "baseline shift", has been suggested to reflect top-down signals that feed back from higher-order control areas to lower-order visual processing areas. Such a shift in baseline activity in visual cortex would presumably "sensitize" neurons with RFs at the attended location, so that when a stimulus subsequently appears at that location there would be enhanced visually evoked activity. Similar effects have also been observed in neuroimaging studies (Kastner et al., 1999), in which "baseline" effects have been observed in areas V1, V2, V4, and TEO. Increases in baseline activity are not only spatially specific, but also appear to depend on the type of visual feature attended to. For instance, Chawla et al. (1999) showed that baseline activity in motion- and color-sensitive areas of human visual cortex (V4 and MT, respectively) was enhanced by selective attention to these visual attributes (see also (Shulman et al., 1999). If our interpretation is correct, it would indicate that top-down signals influence visual processing not only during sustained directed attention to stimulus locations and features, but also during the updating of the information conveyed by endogenous cues. Further experiments are needed to investigate this prediction more explicitly.

3.4. *The role of the PFC and other control regions in top-down attention*

The PFC has long been thought to play an integral role in the control of cognitive processes. Early studies in monkeys (Ferrier, 1876; Bianchi, 1922) and humans (Luria, 1969) described the effects of frontal damage as a disruption of goal-directed behaviors. More recent human lesion studies suggest a broad range of impairments in "executive function" and, in particular, attention (Stuss and Knight, 2002a). The pattern of results obtained by Rossi et al. (2007) suggests that, in the monkey, PFC is most needed for flexibly switching attention from one moment to the next, depending on which stimulus is relevant for the task at hand.

Because the lesions were extensive, it was not possible to localize the region(s) responsible for the deficit. The present study, in humans, which followed the behavioral paradigm studied in the monkey, suggests that the MFG, IFG, and FEF were the most likely sites responsible for the behavioral impairments observed with the monkeys — because these sites exhibited interaction-related activations. Interestingly, our MFG site is situated in what Petrides and Pandya referred to as area 9/46 and area 46 (Petrides and Pandya, 1999), which involve the lower half of the mid-DLPFC in both humans and macaques and are believed to be homologous areas in these two species (e.g., in both species they have a well-developed

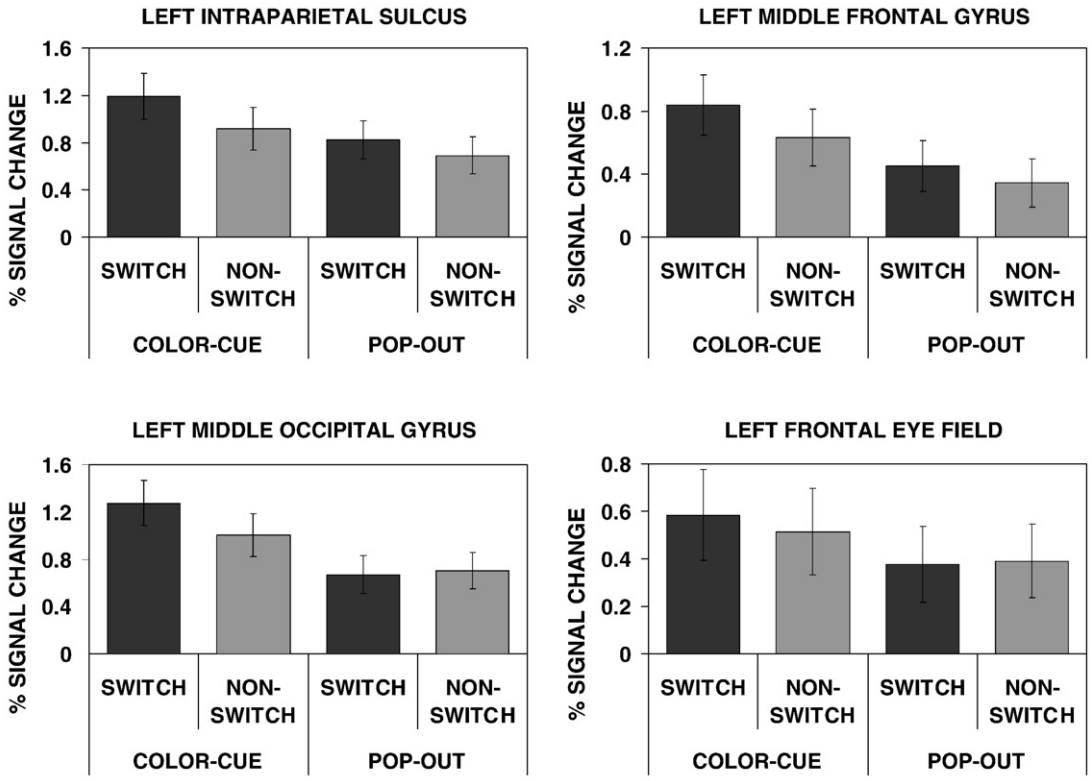

Fig. 4 – Bar plots displaying mean percent signal change as a function of task and trial type for select regions of interest (average over 6-mm radius sphere). Error bars indicate the standard error of the mean.

granular layer IV). Another large portion of PFC removed in the monkey study was area 12 (ventrolateral convexity), which likely corresponds to area 47 in human including the IFG (see also Petrides and Pandya, 1999). In addition, the FEF in the macaque, which is located in Brodmann area 8 (PFC), is believed to be homologous to the FEF in humans, which is located in Brodmann area 6 (premotor cortex); see Beauchamp et al. (2001).

The findings by Rossi et al. suggest that, in the monkey, PFC plays a predominant role in the ability to flexibly switch top-down attention. While our findings agree with theirs insofar as we observed a task by trial type interaction in the PFC, our results also revealed that the parietal cortex is strongly engaged during attentional switching. Indeed, differential responses in the IPS were observed during switch vs. non-switch trials for both the color-cue and the pop-out tasks. Critically, however, IPS engagement during switch trials was stronger during the color-cue task, as revealed by a task by trial type interaction at this site — note that the posterior parietal activation observed in the interaction maps may correspond to parietal area LIP in monkeys (Sereno and Tootell, 2005).

The present study thus suggests that the MFG and FEF, in frontal cortex, and the IPS, in parietal cortex, are important for the top-down updating of cue-related information. These findings are consistent with the notion, recently advanced by Petersen et al. (Dosenbach et al., 2008), that the lateral PFC does not constitute the sole top-down controller in the brain (Miller and Cohen, 2001). Instead, functionally and anatomically distinguishable regions of frontal and parietal cortex contribute specific individual control functions as nodes within separate control networks. In particular, the proposed *dual-networks model* is able to account for the monkey findings (Rossi et al., 2007) that large lateral PFC lesions severely impair the ability of a macaque to adjust behavior in response to frequent cue changes, whereas its ability to maintain set (which is purported to be dependent on dorsal ACC, among other regions) is largely unaffected — by comparison, these results may be problematic for single-mechanism lateral PFC accounts of top-down control. The dual-network framework is also in line with the absence of ACC activation during switch trials in our fMRI study, as this site is posited to be involved in "stable set control" as opposed to "rapid adaptive control".

Finally, the present study also revealed that activations in several visual regions engaged by the oriented gratings were strongly affected by endogenous cue updating, raising the possibility that they were the recipient of top-down signals that are generated when cue information is updated. These findings are consistent with both single- and dual-network models that suggest that sensory processing regions are the target of control signals originating in fronto-parietal regions.

4. Experimental procedures

4.1. *Subjects*

Twenty normal volunteers (6 females) aged 32±5 (SD) years participated in the study, which was approved by the National Institute of Mental Health (NIMH) Institutional Review Board.

All subjects were in good health with no past history of psychiatric and neurological disease and gave informed consent. Subjects had normal or corrected-to-normal vision.

4.2. *Trial, run, and block structure*

Two trial types were employed, both with similar overall structure (Fig. 1). During *color-cue* trials, an initial fixation square was shown for 500 ms, followed by a 500-ms display containing the central cue and the peripheral array of gratings. The middle grating was centered at 6 degrees from fixation; each grating subtended 1°. A red, green, or blue square at fixation served as a cue. The color of the cue indicated the color of the target grating on which the subject was to perform an orientation judgment. Potential targets only comprised the central three locations; the two additional extreme gratings were fixed and were included to equate sensory stimulation with the pop-out condition (see below); these two gratings were shown in yellow or white color. The appearance of the central fixation square (500 ms) then prompted the subject to indicate whether the grating was vertical or off-vertical; responses were made via right-hand button presses. The trial then ended with a 1500-ms blank screen. The total trial duration was therefore 2500 ms. *Pop-out* trials exhibited the same trial structure. The only differences were that the stimulus display contained a single grating whose color differed from that of the remaining four gratings and the central fixation square was white (uninformative cue); gratings were shown in red or green color. Again, only the central three locations served as potential target locations. As described in the Introduction, for both conditions, there were two types of trial: *switch* and *non-switch* trials, which occurred in random order. Note that the target location was randomized on each trial, irrespective of whether the trial was a switch or non-switch trial. For instance, in a sequence of non-switch color-cue trials, although by definition the cue color remained the same, the spatial location of the target grating was random (within the central three locations). Likewise, in a sequence of non-switch pop-out trials, although the color singleton was the same on each trial, its location was random (within the central three locations).

Color-cue and pop-out trials occurred in a blocked fashion and only one condition occurred during a run. Within individual runs, each block of trials lasted 100 s (40 trials). During each block, 5–10 switch trials occurred at random. A 15-s fixation interval separated blocks. Subjects performed alternating runs containing either color-cue or pop-out trials (order counterbalanced across subjects), with each run containing 6 blocks, starting with a 20-s fixation and ending with a 30-s fixation. Thus, subjects performed 240 trials of a given kind in each experimental run. For both color-cue and pop-out trials, grating stimuli were presented in the right visual hemifield. In addition, both informative (color-cue) and non-informative (pop-out) cues were shown centrally (hence leading to activations of visual areas in both hemispheres).

4.3. *fMRI data acquisition and analysis*

fMRI data were collected using a General Electric 3.0 Tesla scanner. Each scanning session began with the acquisition of a high resolution SPGR anatomical sequence. Each subject performed 5–8 experimental runs. During each functional scan, gradient echo echo-planar volumes were acquired with a TE of 30 ms and TR of 2.5 s. Each volume consisted of 24 axial slices with slice thickness of 5 mm and in-plane resolution of 3.75 mm × 3.75 mm.

fMRI data were analyzed using the General Linear Model in AFNI (Cox, 1996). The first 4 volumes of each run were discarded to allow for equilibration effects. Volumes were spatially registered to the volume acquired closest in time to the particular subject's high-resolution SPGR anatomy. Next, each volume was spatially smoothed with an 8-mm Gaussian filter (FWHM). A multiple regression analysis was performed using the four regressors of interest (2 tasks: color-cue and pop-out; 2 trial types: switch and non-switch).

fMRI analyses employed standard multiple regression methods (Friston et al., 1995). The linear models included a constant term and a linear term (for each run) that served as covariates of no interest (these terms controlled for drifts of MR signal across and within runs). For group analyses, each individual's brain was transformed with AFNI into the standard coordinate space of Talairach and Tournoux (1988). To assess the reliability of the results in terms of the population, we performed a mixed-effects analysis in which participant was a random factor and task (color-cue and pop-out) and trial type (switch and non-switch) were fixed factors. For this purpose, a standard two-stage analysis employed the regression coefficients ("parameter estimates") obtained from multiple linear regression for each experimental condition (first stage), which were then employed in subsequent statistical tests (second stage). Regressors for the first stage were formed by convolving stick functions encoding the four trial types with the canonical hemodynamic response function (Cohen, 1997). It is important to note that separate estimates for switch and non-switch trials could be reliably estimated because these trial types occurred randomly within the blocks. In this manner, the intervals between switch and non-switch trials were effectively jittered, which allowed for the deconvolution of the trial responses (Dale, 1999; Birn et al., 2002).

Brain maps in Fig. 2 display the results of a repeated-measures ANOVA of the main effects of color-cue vs. pop-out conditions and of switch vs. non-switch trials; the statistical interaction is shown at the bottom of Fig. 3 ("Interaction" panel). Brain maps in Fig. 3 ("Cue: S vs. NS" and "Pop: S vs. NS" panels) display the results of paired *t* tests contrasting switch to non-switch trials for the color-cue and pop-out conditions. Statistical maps were thresholded at a p value of 0.01 (uncorrected) and displayed on inflated surface brains (N27 anatomical Talairach dataset) created using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). To address the issue of multiple comparisons, in Table 1 and Table 2, we report our results in the following manner. First, we created a mask defined by the contrast of all-task vs. baseline, thresholded at $p<0.001$ (uncorrected). Differential activations from the contrasts above that were observed within this reduced search space are indicated via an asterisk in Table 1 and Table 2. Second, we indicate via a "C" activation sites that survived a cluster-based (5 mm radius) thresholding, which provided a corrected p value of 0.01 at the cluster level, as determined by the AlphaSim tool of the AFNI toolkit.

Acknowledgments

We thank David Sturman and Aurora Ramos for assistance in this project and Ziad Saad for help with surface mapping. This work was supported by the NIMH Intramural Research Program. L.P. was supported in part by R01MH071589 and R. D. was supported in part by 5R01EY017292.

REFERENCES

Asaad, WF, Rainer, G, Miller, EK, 2000. Task-specific neural activity in the primate prefrontal cortex. J. Neurophysiol. 84, 451–459.

Beauchamp, MS, Petit, L, Ellmore, TM, Ingeholm, J, Haxby, JV, 2001. A parametric fMRI study of overt and covert shifts of visuospatial attention. NeuroImage 14, 310–321.

Bianchi, L, 1922. The Mechanisms of the Brain and the Functions of the Frontal Lobes. Livingstone, Edinburgh.

Birn, RM, Cox, RW, Bandettini, PA, 2002. Detection versus estimation in event-related fMRI: choosing the optimal stimulus timing. NeuroImage 15, 252–264.

Braver, TS, Reynolds, JR, Donaldson, DI, 2003. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron 39, 713–726.

Buschman, TJ, Miller, EK, 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315, 1860–1862.

Casey, BJ, Tottenham, N, Fossella, J, 2002. Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control. Dev. Psychobiol. 40, 237–254.

Chawla, D, Rees, G, Friston, KJ, 1999. The physiological basis of attentional modulation in extrastriate visual areas. Nat. Neurosci. 2, 671–676.

Cohen, MS, 1997. Parametric analysis of fMRI data using linear systems methods. NeuroImage 6, 93–103.

Cohen, JD, Botvinick, M, Carter, CS, 2000. Anterior cingulate and prefrontal cortex: who's in control? Nat. Neurosci. 3, 421–423.

Corbetta, M, Shulman, GL, 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.

Corbetta, M, Kincade, JM, Ollinger, JM, McAvoy, MP, Shulman, GL, 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat. Neurosci. 3, 292–297.

Cox, RW, 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.

Dale, AM, 1999. Optimal experimental design for event-related fMRI. Hum. Brain. Mapp. 8, 109–114.

Desimone, R, Duncan, J, 1995. Neural mechanisms of selective attention. Annu. Rev. Neurosci. 18, 193–222.

Dosenbach, NU, Fair, DA, Cohen, AL, Schlaggar, BL, Petersen, SE, 2008. A dual-networks architecture of top-down control. Trends Cogn. Sci. 12, 99–105.

Dreher, JC, Berman, KF, 2002. Fractionating the neural substrate of cognitive control processes. Proc. Natl. Acad. Sci. U. S. A. 99, 14595–14600.

Dreher, JC, Grafman, J, 2003. Dissociating the roles of the rostral anterior cingulate and the lateral prefrontal cortices in performing two tasks simultaneously or successively. Cereb. Cortex 13, 329–339.

Durston, S, Davidson, MC, Thomas, KM, Worden, MS, Tottenham, N, Martinez, A, Watts, R, Ulug, AM, Casey, BJ, 2003. Parametric manipulation of conflict and response competition using rapid mixed-trial event-related fMRI. Neuroimage 20, 2135–2141.

Everling, S, Tinsley, CJ, Gaffan, D, Duncan, J, 2002. Filtering of neural signals by focused attention in the monkey prefrontal cortex. Nat. Neurosci. 5, 671–676.

Ferrier, D, 1876. The Functions of the Brain. Putnam, New York.

Friston, KJ, Holmes, AP, Worsley, KJ, Poline, J-P, Heather, JD, Frackowiak, RS, 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 3, 165–189.

Fuster, JM, 1997. The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobes. Raven, New York.

Giesbrecht, B, Woldorff, MG, Song, AW, Mangun, GR, 2003. Neural mechanisms of top-down control during spatial and feature attention. Neuroimage 19, 496–512.

Hampshire, A, Owen, AM, 2006. Fractionating attentional control using event-related fMRI. Cereb. Cortex 16, 1679–1689.

Hopfinger, JB, Buonocore, MH, Mangun, GR, 2000a. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.

Hopfinger, JB, Buonocore, MH, Mangun, GR, 2000b. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.

Kastner, S, Ungerleider, LG, 2000. Mechanisms of visual attention in the human cortex. Annu. Rev. Neurosci. 23, 315–341.

Kastner, S, Pinsk, MA, De Weerd, P, Desimone, R, Ungerleider, LG, 1999. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron 22, 751–761.

Kincade, JM, Abrams, RA, Astafiev, SV, Shulman, GL, Corbetta, M, 2005. An event-related functional magnetic resonance imaging study of voluntary and stimulus-driven orienting of attention. J. Neurosci. 25, 4593–4604.

Luck, SJ, Chelazzi, L, Hillyard, SA, Desimone, R, 1997. Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J. Neurophysiol. 77, 24–42.

Luria, AR, 1969. Frontal lobe syndromes. In: Vinken, PJ, Bruyn, GW (Eds.), Handbook of Clinical Neurology. Elsevier, New York, pp. 725–757.

MacDonald III, AW, Cohen, JD, Stenger, VA, Carter, CS, 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835–1838.

Marois, R, Chun, MM, Gore, JC, 2000. Neural correlates of the attentional blink. Neuron 28, 299–308.

Marois, R, Chun, MM, Gore, JC, 2004. A common parieto-frontal network is recruited under both low visibility and high perceptual interference conditions. J. Neurophysiol. 92, 2985–2992.

Mayer, AR, Dorflinger, JM, Rao, SM, Seidenberg, M, 2004. Neural networks underlying endogenous and exogenous visual-spatial orienting. Neuroimage 23, 534–541.

Miller, EK, 2000. The prefrontal cortex and cognitive control. Nat. Rev. Neurosci. 1, 59–65.

Miller, EK, Cohen, JD, 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.

Peers, PV, Ludwig, CJ, Rorden, C, Cusack, R, Bonfiglioli, C, Bundesen, C, Driver, J, Antoun, N, Duncan, J, 2005. Attentional functions of parietal and frontal cortex. Cereb. Cortex 15, 1469–1484.

Pessoa, L, Kastner, S, Ungerleider, LG, 2003. Neuroimaging studies of attention: from modulation of sensory processing to top-down control. J. Neurosci. 23, 3990–3998.

Petrides, M, Pandya, DN, 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur. J. Neurosci. 11, 1011–1036.

Rosen, AC, Rao, SM, Caffarra, P, Scaglioni, A, Bobholz, JA, Woodley, SJ, Hammeke, TA, Cunningham, JM, Prieto, TE, Binder, JR, 1999. Neural basis of endogenous and exogenous spatial orienting: a functional MRI study. J. Cogn. Neurosci. 11, 135–152.

Rossi, AF, Bichot, NP, Desimone, R, Ungerleider, LG, 2007. Top-down attentional deficits in macaques with lesions of lateral prefrontal cortex. J. Neurosci. 17, 11306–11314.
Serences, JT, Yantis, S, 2006. Selective visual attention and perceptual coherence. Trends Cogn. Sci. 10, 38–45.
Sereno, MI, Tootell, RB, 2005. From monkeys to humans: what do we now know about brain homologies? Curr. Opin. Neurobiol. 15, 135–144.
Shomstein, S, Behrmann, M, 2006. Cortical systems mediating visual attention to both objects and spatial locations. Proc. Natl. Acad. Sci. U. S. A. 103, 11387–11392.
Shulman, GL, Ollinger, JA, Akbudak, E, Conturo, TE, Snyder, AZ, Petersen, SE, Corbetta, M, 1999. Areas involved in encoding and applying directional expectations to moving objects. J. Neurosci. 21, 9480–9496.
Slagter, HA, Weissman, DH, Giesbrecht, B, Kenemans, JL, Mangun, GR, Kok, A, Woldorff, MG, 2006. Brain regions activated by endogenous preparatory set shifting as revealed by fMRI. Cogn. Affect Behav. Neurosci. 6, 175–189.
Stuss, D, Knight, RT (Eds.), 2002a. Principles of Frontal Lobe Function. Oxford University Press, Oxford.
Stuss, DT, Knight, RT (Eds.), 2002b. Principles of Frontal Lobe Function. Oxford University Press, New York.
Talairach, J, Tournoux, P, 1988. Co-planar stereotaxis atlas of the human brain. Thieme Medical, New York.
White, IM, Wise, SP, 1999. Rule-dependent neuronal activity in the prefrontal cortex. Exp. Brain Res. 126, 315–335.
Yantis, S, Serences, JT, 2003. Cortical mechanisms of space-based and object-based attentional control. Curr. Opin. Neurobiol. 13, 187–193.